REMARKS

Claims 6, 9, 10, 12-22, 28-34, and 36-45 were pending in the application. Claims 9, 39-41 and 43 have been amended. New claim 46 has been added. Accordingly, upon entry of the foregoing Amendment and Response, claims 6, 9, 10, 12-22, 28-34, and 36-46 will be pending in the application.

Support for the amendment to claim 43 and new claim 46 can be found throughout the specification, including at least at page 8, line 15 and in Table IV. Support for the amendments to claims 39 and 40 can be found throughout the specification, including at least at page 24, lines 20-21 and pages 33-35. The foregoing amendments introduce no new matter and are not related to issues of patentability.

The foregoing claim amendments should in no way be construed as an acquiescence to any of the Examiner's restrictions and were made solely to expedite prosecution of the present application. Entry of the foregoing Amendment and Response is respectfully in order and requested. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

Restriction Under 35 U.S.C. 121

The Examiner has required restriction to one of the following inventions as required under 35 U.S.C. 121:

Group I: Claims 6, 9, 10, 17, 28-34, 36, 38-43 drawn to a recombinant inhibitor protein of a kallikrein comprising a serpin sequence wherein the Reactive Serpin Loop (RSL) of the serpin sequence is modified by at least one substrate active site sequence, fragments thereof, a molecular chimera thereof, a combination thereof, and variants thereof, specific for said kallikrein, and a diagnostic kit for the detection of a kallikrein in a specimen comprising the recombinant inhibitor protein of claim 39;

Group II: Claims 12-16, 37, 44 and 45, drawn to an isolated DNA sequence encoding the recombinant inhibitor protein of claim 39, and a diagnostic kit for the detection of a kallikrein in a specimen comprising DNA sequence selected from the group consisting of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, a sequence complementary thereof, fragment thereof, and variants thereof; and

Group III: Claims 18-22, drawn to a method of treating or preventing a proteolysis-associated disorder in a mammal comprising administering to said mammal the pharmaceutical composition of claim 17.

Applicants traverse the restriction of Groups I-III on the grounds that restriction of the claims is improper based on the unity of the invention determined during the international stage of the instant application, and, furthermore, that the art cited by the Examiner does not teach the general inventive concept of the amended claims.

As amended, the claims are directed to a recombinant inhibitor protein, or an inhibiting fragment thereof, specific for a kallikrein, comprising a serpin sequence comprising ***a modified Reactive Serpin Loop (RSL), wherein the modified RSL is modified by at least one substrate active site sequence resulting in increased binding affinity for said kallikrein***, *e.g.*, the kallikrein hK2. The amended claims are also directed to a recombinant inhibitor protein, or an inhibiting fragment thereof, specific for a kallikrein, comprising a serpin sequence comprising ***a modified Reactive Serpin Loop (RSL), wherein the amino acid sequence of the modified RSL is selected from the group consisting of SEQ ID No 16, 17, 18, 19, 20, 21, and 22***. The invention is further directed to a recombinant inhibitor protein, or an inhibiting fragment thereof, specific for a kallikrein, comprising a serpin sequence ***comprising a modified Reactive Serpin Loop (RSL), wherein the P6 – P6' region of the RSL is modified by at least one substrate active site sequence.***

Chao *et al.* describes the tissue expression pattern of endogenous kallistatin, a member of the serpin superfamily which binds kallikrein. Applicants submit that in contrast to the Examiner's assertion, Chao *et al.* does not anticipate the claimed invention because the cited reference fails to teach the "special technical feature" of the claimed invention. The invention is directed to a recombinant inhibitor protein, or an inhibiting fragment thereof, specific for a kallikrein, comprising a serpin sequence comprising a ***modified RSL***. As described in the specification, the invention relates to an inhibitor protein comprising a modified RSL region, wherein a sequence, *e.g.*, a preferential recognition site for a protease, is changed in order to provide an inhibitor protein having improved binding for the target protease, *e.g.*, kallikrein. The pending claims all relate to the general inventive concept of the invention, *i.e.*, a recombinant inhibitor protein which inhibits a kallikrein, where the recombinant inhibitor protein has a modified RSL which is modified at a sequence such that the recombinant inhibitor

protein is specific for a kallikrein. Chao *et al.* teaches native kallistatin and does not teach modifying the RSL of kallistatin. Accordingly, a finding that there is lack of unity within the amended claims is improper, as the claimed invention is novel over Chao *et al.*

Furthermore, Applicants respectfully traverse the Restriction Requirement as a whole on the ground that the requirement conflicts with the finding of unity during the international stage of the instant application. Specifically, Applicants note that during the international phase of International Application No. PCT/IB2004/001040, of which the present case is a 35 U.S.C. §371 national phase application, the International Searching Authority did not find lack of unity among the claims. For the convenience of the Examiner, Applicants enclose herewith a copy of the International Search Report (enclosed herewith as Appendix A) and the International Preliminary Report on Patentability (IPRP) (enclosed herewith as Appendix B) which describe the unity of invention decision from the international application. As indicated at page 2 of the attached IPRP (Appendix B), there was no lack of unity of invention found for the corresponding PCT application. Applicants also submit herewith Appendix C, which contains a listing of the pending claims in the present application and the corresponding claims from the international application.

In order to be responsive, however, Applicants hereby elect the Group I invention (claims 6, 9, 10, 17, 28-34, 36, 38-43).

The Examiner has further restricted the Group I invention to the following groups:

Group A: MD820;

Group B: MD62;

Group C: MD61;

Group D: MD67; and

Group E: MDCI.

Applicants hereby traverse the restriction of Groups A-E on the grounds that the Restriction Requirement as a whole is improper and conflicts with the finding of unity during the international stage of the instant application (as described above).

In addition, Applicants assert that the subject matter of Groups A-E (claims 35-37) represent different embodiments of a single inventive concept which merit examination in a single application. ***The inhibitor proteins described in Groups A-E are no less than about 99% identical to one another and represent a single inventive concept.*** The recombinant inhibitor

proteins described in claim 10, *i.e.*, Groups A-E, refer to proteins having a high degree of identity to one another. As described in the specification, each of the proteins described in Groups A-E is a variant of the ACT protein having between 2-6 amino acid substitutions within the RSL region (see Figure 7A (MD 820), Figure 7B (MD 62), Figure 7D (MD 67), Figure 7E (MD 61), and Figure 7G (MDCI)). The P6-P6'RSL sequences of the inhibitor proteins of Groups A-E are also shown in Figure 8.

Applicants also note that an allowable generic claim (*i.e.*, claim 39, as amended) has been provided which links Groups A-E. Applicants respectfully submit that restriction among Groups A-E is improper as generic claim 39 links the species recited in Groups A-E. Applicants respectfully request that restriction under 35 U.S.C. §121 between groups A-E be reconsidered. If the restriction of Groups I-III is maintained, Applicants respectfully suggest that groups A-E be re-grouped as a unified group subject to a species election

In order to be responsive, however, Applicants hereby elect the Group D invention (MD 67).

For the foregoing reasons, Applicants respectfully request the withdrawal of the present Restriction Requirement.

While Applicants traverse the restriction of the claims as a whole for the reasons set forth above, in order to be responsive Applicants provide the following with respect to the species election. The Examiner has required that Applicants elect a species of the claimed invention of Group I from the following list:

- a single serpin sequence as listed in claim 9; and
- one sequence from the group consisting of SEQ ID NOs: 16, 17, 18, 19, 20, 21 or 22.

Applicants elect the species of serpin sequence, α-lantichymotrypsin (ACT). Claims which are readable on the elected species include claims 6, 9, 10, 12-22, 28-34, and 36-45.

With respect to the election of a sequence selected from the group consisting of SEQ ID NOs: 16, 17, 18, 19, 20, 21 or 22, Applicants note that SEQ ID NOs: 16, 17, 18, 19, 20, 21 or 22 represent modified RSLs, and are described in Figure 8 of the specification. More specifically, for example, SEQ ID NO: 16 corresponds to the P6-P6' region of protein MD820; SEQ ID NO: 17 corresponds to the P6-P6' region of protein MD62, and so forth. As such, the restriction of group A-E and the species election of SEQ ID NOs: 16 to 22 is inconsistent, as SEQ ID NOs: 16

to 22 correspond to the modified RSL region of the recombinant inhibitor proteins described in Groups A-E. If the restriction of Groups I-III is maintained, Applicants respectfully suggest that groups A-E be re-grouped with the respective sequences described in SEQ ID NOs: 16-22 as a single species election. Applicants hereby elect SEQ ID NO: 19 as the species of sequence recited in claim 41. Claims which are readable on the elected species include claims 6, 9, 10, 12-22, 28-34, and 36-45.

With respect to the elected species, it is Applicants understanding that the election of a species and specific species is for searching purposes only. It is also Applicants understanding that upon allowance of the elected claims, the generic claims also will be searched and Applicants will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 C.F.R. § 1.141. Applicants hereby reserve the right to traverse the species and specific species elections if Applicants' understanding is incorrect.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 12-0080, under Order No. KZI-003US.

Dated: March 13, 2007

Respectfully submitted,

By _____

Cristin E. Howley, Ph.D.
Registration No.: 55,281
LAHIVE & COCKFIELD, LLP
One Post Office Square
Boston, Massachusetts 02109
(617) 227-7400
(617) 742-4214 (Fax)
Attorney For Applicants

PATENT COOPERATION TREATY

Appendix A

14 OCT. 2004

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:
KATZAROV S.A.
19, rue des Epinettes
CH-1227 Geneva
SWITZERLAND

COMMUNICATION IN CASES FOR WHICH
NO OTHER FORM IS APPLICABLE

Applicant's or agent's file reference 14542-PCT	Date of mailing *(day/month/year)* 12/10/2004
International application No. PCT/IB2004/001040	**REPLY DUE** See paragraph 1 below
Applicant UNIVERSITE DE LAUSANNE	International filing date *(day/month/year)* 05/04/2004

1. [ ] REPLY DUE within _____ ~~months~~/days from the above date of mailing

   [X] NO REPLY DUE

2. COMMUNICATION:

The international search report and written opinion of the ISA mailed to you on 25.08.04 contained the following incorrect IPC symbol :

A61K37/64 .

Please find enclosed new forms PCT/ISA/210 and PCT/ISA/237 which replace the ones already in your possession.

We wish to apologize for any inconvenience caused.

A copy of this letter and its enclosures has been sent to the International Bureau in Geneva.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Wolfgang-Peter Schießl

Form PCT/ISA/224 (January 1994)

CORRECTED VERSION

. ATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

To:
KATZAROV S.A.
19, rue des Epinettes
CH-1227 Geneva
SWITZERLAND

Date of mailing *(day/month/year)*	12/10/2004
Applicant's or agent's file reference: 14542-PCT	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No.: PCT/IB2004/001040	International filing date *(day/month/year)*: 05/04/2004
Applicant: UNIVERSITE DE LAUSANNE	

1. [x] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Fascimile No.: (41-22) 740.14.35

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until **30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Wolfgang-Peter Schießl

(See notes on accompanying sheet)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims,description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

PATENT COOPERATION TREATY

CORRECTED VERSION

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
14542-PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IB2004/001040	05/04/2004	04/04/2003
Applicant		
UNIVERSITE DE LAUSANNE		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 07 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
      [ ] The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. [X] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box II).

3. [ ] **Unity of invention is lacking** (see Box III).

4. With regard to the **title,**
   [ ] the text is approved as submitted by the applicant.
   [X] the text has been established by this Authority to read as follows:
   INHIBITOR PROTEINS OF A PROTEASE AND USE THEREOF

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regards to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. 4a, 4b
      [X] as suggested by the applicant.
      [ ] as selected by this Authority, because the applicant failed to suggest a figure.
      [ ] as selected by this Authority, because this figure better characterizes the invention.
   b. [ ] none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2004/001040

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:

   a. type of material

   [X] a sequence listing

   [ ] table(s) related to the sequence listing

   b. format of material

   [ ] in written format

   [ ] in computer readable form

   c. time of filing/furnishing

   [ ] contained in the international application as filed

   [ ] filed together with the international application in computer readable form

   [ ] furnished subsequently to this Authority for the purpose of search

2. [ ] In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2004/001040

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 18-22
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 18-22 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2004/001040

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/09 C12N15/15 C12P21/02 C12N9/64

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C12P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 827 662 A (COOPERMAN BARRY ET AL) 27 October 1998 (1998-10-27) column 6, lines 48-67, Table I and II and claims 1-6	1-3,5, 7-9,12, 14-17, 23,25, 26, 28-36,38

X	WO 95/27053 A (UNIV PENNSYLVANIA) 12 October 1995 (1995-10-12) page 4, first paragraph, page 14, last paragraph	1-3,5, 7-9,12, 14-17, 23,25, 28-36,38

	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 October 2004	12. 10. 04

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Simm, M.D.

Form PCT/ISA/210 (second sheet) (January 2004)

International Application No
PCT/IB2004/001040

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JANCIAUSKIENE S: "Conformational properties of serine proteinase inhibitors (serpins) confer multiple pathophysiological roles" BIOCHIMICA ET BIOPHYSICA ACTA. MOLECULAR BASIS OF DISEASE, AMSTERDAM, NL, vol. 1535, no. 3, 26 March 2001 (2001-03-26), pages 221-235, XP004277055 ISSN: 0925-4439 the whole document	1-38
T	BOS I G A ET AL: "Effect of reactive site loop elongation on the inhibitory activity of C1-inhibitor" BIOCHIMICA ET BIOPHYSICA ACTA, vol. 1699, no. 1-2, 1 June 2004 (2004-06-01), pages 139-144, XP004509918 the whole document	1-38
A	EP 1 029 921 A (UNIV TEXAS) 23 August 2000 (2000-08-23) the whole document	1-38

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB2004/001040

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5827662 A	27-10-1998	US 5612194 A	18-03-1997
		US 5723316 A	03-03-1998
		US 5674708 A	07-10-1997
		US 5367064 A	22-11-1994
		US 5079336 A	07-01-1992
		AU 2382195 A	10-11-1995
		BG 100981 A	30-01-1998
		BR 9507467 A	23-09-1997
		CA 2188180 A1	26-10-1995
		CN 1146207 A	26-03-1997
		CZ 9603003 A3	13-08-1997
		EP 0765342 A1	02-04-1997
		FI 964174 A	17-10-1996
		HU 75358 A2	28-05-1997
		JP 10501404 T	10-02-1998
		LV 11801 A	20-06-1997
		NO 964416 A	17-10-1996
		OA 10727 A	09-12-2002
		PL 316949 A1	17-02-1997
		SI 9520043 A	31-08-1997
		SK 130696 A3	09-07-1997
		WO 9528422 A1	26-10-1995
		US 5637479 A	10-06-1997
		LT 96158 A	25-06-1997
		AU 696945 B2	24-09-1998
		AU 6715694 A	23-10-1995
		CA 2186635 A1	12-10-1995
		EP 0757719 A1	12-02-1997
		JP 9512422 T	16-12-1997
		WO 9527053 A1	12-10-1995
		AU 696995 B2	24-09-1998
		AU 7393694 A	23-10-1995
		BG 100939 A	31-10-1997
		CA 2186908 A1	12-10-1995
		CN 1145637 A	19-03-1997
		CZ 9602817 A3	14-05-1997
		EP 0754228 A1	22-01-1997
		FI 963891 A	27-09-1996
		HU 74901 A2	28-02-1997
		JP 9512423 T	16-12-1997
		LV 11747 A	20-04-1997
		LV 11747 B	20-10-1997
		NO 964022 A	24-09-1996
		NZ 269619 A	26-01-1998
		PL 316433 A1	06-01-1997
		SI 9420082 A	30-06-1997
		SK 138196 A3	09-07-1997
		WO 9527055 A1	12-10-1995
		US 5266465 A	30-11-1993
WO 9527053 A	12-10-1995	US 5723316 A	03-03-1998
		AU 696945 B2	24-09-1998
		AU 6715694 A	23-10-1995
		CA 2186635 A1	12-10-1995
		EP 0757719 A1	12-02-1997
		JP 9512422 T	16-12-1997
		WO 9527053 A1	12-10-1995
		US 5612194 A	18-03-1997

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB2004/001040

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9527053 A		US 5637479 A	10-06-1997
		US 5827662 A	27-10-1998
EP 1029921 A	23-08-2000	US 5550042 A	27-08-1996
		EP 1029921 A1	23-08-2000
		AT 226636 T	15-11-2002
		AT 199090 T	15-02-2001
		AU 637791 B2	10-06-1993
		AU 5278090 A	09-10-1990
		CA 2047702 A1	07-09-1990
		DE 69033699 D1	15-03-2001
		DE 69033699 T2	23-05-2001
		DE 69034013 D1	28-11-2002
		DE 69034013 T2	31-07-2003
		DK 1029921 T3	24-02-2003
		DK 462207 T3	18-06-2001
		EP 0462207 A1	27-12-1991
		ES 2185529 T3	01-05-2003
		ES 2154629 T3	16-04-2001
		JP 3076034 B2	14-08-2000
		JP 2000078990 A	21-03-2000
		JP 3076035 B2	14-08-2000
		JP 2000037195 A	08-02-2000
		JP 2991769 B2	20-12-1999
		JP 4504952 T	03-09-1992
		WO 9010649 A1	20-09-1990
		US 5486602 A	23-01-1996
		US 5304482 A	19-04-1994
		US 5728564 A	17-03-1998
		US 5866413 A	02-02-1999

PATENT COOPERATION TREATY

CORRECTED VERSION

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2004/001040	05.04.2004	04.04.2003

International Patent Classification (IPC) or both national classification and IPC
C12N15/09, C12N15/15, C12P21/02, ~~A61K37/64~~, C12N9/64

Applicant
UNIVERSITE DE LAUSANNE

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Simm, M.D. Telephone No. +49 89 2399-7411

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 18-22

because:

☒ the said international application, or the said claims Nos. 18-22 in respect of i.a. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 18-22

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4,6,10,11, 13, 24,27, 37
	No:	Claims	1-3,5,7-9,12,14-17,23, 25,26,28-36,38
Inventive step (IS)	Yes:	Claims	4,6,10,11,13,37
	No:	Claims	6,24,27
Industrial applicability (IA)	Yes:	Claims	1-17,23-38
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III.

Claims 18-22 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V.

1 The following documents are referred to in this communication:

D1 : US 5 827 662 A (COOPERMAN BARRY ET AL) 27 October 1998 (1998-10-27)

D2 : WO 95/27053 A (UNIV PENNSYLVANIA) 12 October 1995 (1995-10-12)

2 INDEPENDENT CLAIM 1

2.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT.

Document D1 (see column 6, lines 48-67, Table I and II and claims 1-6) discloses a method of producing recombinant serine protease inhibitors (antichymotripsin variants) capable of effectively modulating serine protease activity. The inhibitor comprises a hinge region of a reactive loop which have modified aminoacid sequences (positions 349-368).
The compositions are specially useful in regulating inflammatory processes related to serine proteases accumulating in cells or tissues: tumour migration is mentioned among others (claim 3).
Similarly, D2 (page 4, first paragraph and page 14, last paragraph) discloses antichymotypsin analogue shaving aminoacid substitutions at positions 356-361, useful in the treatment of lung inflammation among others.

Thus, in view of D1-D2 the present claim 1 and the dependent claims 2-4,5,7,8,9 is not novel.

3 INDEPENDENT CLAIMS 12,14,16, 17, 23 and 28

These independent claims would be novel and inventive only when referring to a novel an inventive inhibitor protein, because D1-D2 comprise as well the isolated DNA encoding for the recombinant inhibitor protein, the expression vector, the cells, the pharmaceutical compositions (or strong indications), the medical use the method of producing the inhibitor and diagnostic kits.

Moreover, the subject-matter of dependent claims 15,25,26, 29-36 is as well disclosed in D1-D2 or is common procedure in the field.

4 The sequences corresponding to SEQID N° 1-22 are novel. The exact mutations of RSL sequences 16-22 have not been found in the prior art. These specific recombinant ACT inhibitors are in view of the examples of the present application more specific to a targeted serin protease as the wild-type ACT. Thus, specific recombinant ACT inhibitors appear to be inventive.

5 Claims 1-3 and 5 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.

Claims 1-3 are not supported by the description as required by Article 6 PCT, as its/their scope is broader than justified by the description and drawings. The use of the word "chimeric" in the present invention is not justified, the proteins claimed are not chimeras (two different genes as origin of the protein) but just recombinant variants of ACT.

6 The subject-matter of claims 6, 24 and 27 although formally new, would only appear to be inventive when combined with the claims related to novel and inventive inhibitor protein of protease (Art. 33(3) PCT).

\TENT COOPERATION TRE Y

Appendix B
- 3 OCT. 2005

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

Corrected version

To:

PFEND, Gilles
KATZAROV S.A.
19, rue des Epinettes
CH-1227 Genève
SUISSE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	29.09.2005
Applicant's or agent's file reference: 14542-PCT	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2004/001040	05.04.2004	04.04.2003

Applicant
UNIVERSITE DE LAUSANNE et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Rauf, A Tel. +49 89 2399-7548

Form PCT/IPEA/416 (January 2004)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
14542-PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2004/001040	05.04.2004	04.04.2003

International Patent Classification (IPC) or national classification and IPC
C12N15/09, C12N15/15, C12P21/02, C12N9/64

Applicant
UNIVERSITE DE LAUSANNE et al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 5 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
04.02.2005	29.09.2005

Name and mailing address of the international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Simm, M.D.

Telephone No. +49 89 2399-7411

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IB2004/001040

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-39	as originally filed
Claims, Numbers	
1-38	received on 08.02.2005 with letter of 04.02.2005
Drawings, Sheets	
1/15-15/15	as originally filed

   ☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 18-22

because:

☒ the said international application, or the said claims Nos. 18-22 in respect of i.a. relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 18-22

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4,13, 24,27, 37
	No:	Claims	1-3,5-12,14-17,23, 25,26,28-36,38
Inventive step (IS)	Yes:	Claims	4,13,37
	No:	Claims	6,10,11, 24,27
Industrial applicability (IA)	Yes:	Claims	1-17,23-38
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed

   ☐ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment on

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

Re Item III.

Claims 18-22 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V.

1 The following documents are referred to in this communication:
D1 : US 5 827 662 A (COOPERMAN BARRY ET AL) 27 October 1998 (1998-10-27)
D2 : WO 95/27053 A (UNIV PENNSYLVANIA) 12 October 1995 (1995-10-12)

2 INDEPENDENT CLAIM 1

2.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT.

Document D1 (see column 6, lines 48-67, Table I and II and claims 1-6) discloses a method of producing recombinant serine protease inhibitors (antichymotripsin variants) capable of effectively modulating serine protease activity. The inhibitor comprises a hinge region of a reactive loop which have modified aminoacid sequences (positions 349-368). Kallikrein is mentioned on column 10, lines 5 and 13.
The compositions are specially useful in regulating inflammatory processes related to serine proteases accumulating in cells or tissues: tumour migration is mentioned among others (claim 3).
Similarly, D2 (page 4, first paragraph and page 14, last paragraph) discloses antichymotypsin analogue shaving aminoacid substitutions at positions 356-361, useful in the treatment of lung inflammation among others.

Thus, in view of D1-D2 the present claim 1 and the dependent claims 2-3,5,7,8,9 are not novel.

3 INDEPENDENT CLAIMS 12,14,16, 17, 23 and 28

These independent claims would be novel and inventive only when referring to a novel an inventive inhibitor protein, because D1-D2 comprise as well the isolated DNA encoding for the recombinant inhibitor protein, the expression vector, the cells, the pharmaceutical compositions (or strong indications), the medical use the method of producing the inhibitor and diagnostic kits.

Moreover, the subject-matter of dependent claims 15,25,26, 29-36 is as well disclosed in D1-D2 or is common procedure in the field.

4 The sequences corresponding to SEQID N° 1-22 are novel. The exact mutations of RSL sequences 16-22 have not been found in the prior art. These specific recombinant ACT inhibitors are in view of the examples of the present application more specific to a targeted serin protease as the wild-type ACT. Thus, specific recombinant ACT inhibitors appear to be inventive.

5 Claims 1-3 and 5 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.

Claims 1-3 are not supported by the description as required by Article 6 PCT, as its/their scope is broader than justified by the description and drawings. The use of the word "chimeric" in the present invention is not justified, the proteins claimed are not chimeras (two different genes as origin of the protein) but just recombinant variants of ACT.

6 The subject-matter of claims 6, 24 and 27 although formally new, would only appear to be inventive when combined with the claims related to novel and inventive inhibitor protein of protease (Art. 33(3) PCT).

APPENDIX C

Currently Pending Claim in U.S. Patent Application No. 10/552,786	Corresponding Related Claim during International Phase of International Application No. PCT/IB2004/001040
6	6
9	9
10	10
12	12
13	13
14	14
15	15
16	16
17	17
18	18
19	19
20	20
21	21
22	22
28	28
29	29
30	30
31	31
32	32
33	33
34	34
36	36
37	37
38	38
39	1-3
40	6
41	4
42	29
43	1-3
44	12
45	12